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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,853	04/18/2005	Gilda De Luca	206,953	3983

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,853	DE LUCA ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31,34-45,55-75 and 79-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31, 34-45, 55-75 and 79-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 5/29/2208 has been received, entered and carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 32-33, 46-54 and 76-78 have been canceled.

2. New Claims 80-86 have been added.

3. Claims 37-38, 55, 58-59, 68, 70 and 79 have been amended.

4. Remarks drawn to objections and rejections under 35 USC 112, first and second paragraphs and 103 and Declaration under 35 CFR 1.132 by Anna Zanellato.

Claims 1-31, 34-45, 55-75 and 79-86 are pending in the case.

The objection regarding the Abstract and Schemes 6-7 and 18 in the specification have been overcome by appropriate corrections.

The objection to Claims 32-33 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim has been rendered moot by cancellation of the said claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 46-47 and 76 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising hyaluronic acid

covalently bonded to a taxane and further comprising interferon and the treatment of rheumatoid arthritis, Hashimoto's thyroiditis, systemic lupus erythematosus and glomerulonephritis, does not reasonably provide enablement for a pharmaceutical composition comprising hyaluronic acid covalently bonded to a taxane and further comprising the biologically or pharmaceutically active substances as broadly recited in instant claims 46-47 and the treatment of any auto-immune pathology as broadly encompassed by instant claim 76, has been rendered moot by cancellation of the said claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claims 37-38, 55, 58-59, 63, 68, 70, 73 and 78 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been overcome by amendments and cancellation of claim 78.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of Claims 1-31, 34-45, 55-75 and 79-86 under 35 U.S.C. 103(a) as being unpatentable over Luo et al (Bioconjugate Chem. 1999, 10, 755-763; document AR cited in IDS of Oct. 03, 2005) in view of Sparer et al (Controlled Release Delivery Systems, Chapter 6, 1983, 107-119; document AS cited in IDS of Oct. 03, 2005), Li et al (US 5,977,163) and Desai et al (US 5,648,506; document AC cited in the IDS of Oct. 03, 2005) is being maintained for reasons of record.

Applicants' have traversed the rejection arguing that:

1. The Declaration of Zanellato compares the data in Example 2 transformed as a function of the Taxol equivalent with the data reported by Luo et al using mathematical formula.

Luo et al studied the antitumor activity of taxol linked to hyaluronic acid (HA) by means of adipic hydrazide. From Table 2 of Luo it can be seen that by increasing the taxol loadings the solubility diminishes. HA-taxol containing a Taxol loading of 5% is twice as effective as Taxol itself and that these results are not statistically significant as admitted by Luo. Even though Luo teaches advantages of the said conjugates the experimental results of Luo are poor and would not be viewed as promising.

2. Sparer et al discloses conjugates with different active ingredients from paclitaxel, namely the antibiotic chloramphenicol and cysteine. In Sparer there is nothing that suggests a possible involvement of the glycosaminoglycans, in particular that of HA in increasing the therapeutic activity.

3. Li discloses different conjugated Taxol from those claimed instantly, since HA in Li's conjugate is replaced by a polyaminoacid or polyethylene glycol.

4. The Desai reference discloses a polymeric drug delivery system in which the drug is bound to a water soluble polymer to provide a form of soluble drug delivery.

Applicants' arguments and the analysis provided in Zanellato's Declaration have been considered but are not found to be persuasive.

Based on the detailed mathematical calculations and the statistical significance disclosed in the Declaration applicants conclude that HA-taxol containing a Taxol loading of 5% is twice as effective as Taxol itself and that these results are not statistically significant as admitted by Luo. Well, this particular result may not be statistically significant. But one of skill in the art looking at just this result will not conclude that such conjugates are not useful at all. Since a 5% loading of Taxol in the said HA-taxol is twice as effective as Taxol itself this result call for a

further investigation of the percentage of Taxol loading that would give the optimum beneficial effect of the HA-taxol conjugate. This will not be viewed as a result that is not promising. The result is not promising only if the said HA-taxol conjugate is less active compared to taxol itself.

Sparer et al, drawn to polysaccharide-drug complexes, teaches glycosaminoglycans including hyaluronic acid are drug carriers because of their favorable properties and have various functional groups available for forming different types of bonds with drugs (page 108, line 1 through page 109, line 3). Sparer reports especially the performance of amide and ester linked glycosaminoglycan drug complexes (page 109, 4-7), which are prepared via standard coupling reaction of the carboxyl group of the hyaluronic acid to the hydroxyl and the amino group of the drug (page 112). According to Sparer's study the release rate from amide complexes was slower and gave a prolonged constant release of the drug. Sparer teaches that the rate of release may in principle be engineered by the judicious choice of drug-glycosaminoglycan bond based on the hydrolytic stability of the bond (page 117, last paragraph). This means that drug-glycosaminoglycan complexes containing bonds other than amide and ester may be important in controlled release and should be made and studied with respect to their hydrolysis including the ester, acetal, ketal, urethane and thiourethane bonds as instantly claimed. Even though Sparer does not teach a complex of glycosaminoglycans with Taxol, one of skill in the art will recognize from his teaching that the same could be done using hyaluronic acid and Taxol conjugate containing such linkages since both have several functional groups and different types of bonds could be formed between the two molecules with and without a spacer.

Li et al, drawn to Taxol complexes, teaches water-soluble complexes of paclitaxel and docetaxel with polyethylene glycol polymers (col. 1, lines 5-14). Their complexes are effective

against cancers (col. 5, lines 13-18) and arthritis (col. 5, lines 43-65), and also useful for inhibiting restenosis and coating medical devices like stents (col. 5, line 66 through col. 6, line 43). According to Li such complexes improve the efficacy of anticancer therapy by providing water-soluble and controlled release paclitaxel derived compositions and also eliminate the need for solvents that are associated with side effects (col. 8, lines 34-41). Even though Li et al do not teach Taxol hyaluronic acid conjugates, one of skill in the art would recognize from their teaching that conjugates containing HA and Taxol can also be used in a method of treatment of cancers, tumors, and restenosis and for coating medical devices.

Desai, drawn to Taxol-carrier conjugates, teaches a process for the attachment of Taxol to carriers via different types of covalent linkages like ester, urethane, amide, amine and ether etc. (urethane and acetal and ketal linkages are instantly claimed. The ether linkage taught by Desai is similar to the acetal and ketal linkage; col. 4, lines 19-36 and examples 1-5). Even though Desai et al do not exemplify such conjugates using Taxol and hyaluronic acid as instantly claimed, one of skill in the art will recognize that the same type of process steps can be used in the instant process for making Taxol-hyaluronic acid complexes comprising different types of linkages as instantly claimed. Taxol and hyaluronic acid have functional groups that could be advantageously used for making different types of linkages as instantly claimed. From the point of view of making complexes using different type of linkages Sparer's and Desai's teachings are relevant and one of skill in the art will definitely look to these for applying the teachings to the compositions and methods as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a taxane covalently bonded to hyaluronic acid optionally using a spacer, and

use them in a method of treatment and as a coating for medical devices since closely analogous complexes comprising the active agents and their use in treating cancer, restenosis and as coating for medical devices is seen to be taught in the prior art.

One of skill in the art would be motivated to make the complexes as instantly claimed via the process as instantly claimed and use them in a method of treatment as instantly claimed and in coating medical devices since Taxol and hyaluronic acid have many functional groups which makes it possible to make complexes via different type of bonds, which according to Sparer could lead to drug complexes with varied release times, which in turn would extend the duration of treatment. Complexation with hyaluronic acid has the advantage of biocompatibility and also selectivity to cancer cells because of the overexpression of receptors of hyaluronic acid by these cells. The presence of several functional groups in both the agents also helps to make different types of bonds that link both the agents to each other with and without a spacer. One of skill in the art would also look at different percentages of Taxol loading for optimizing the beneficial effects.

Conclusion

Claims 1-31, 34-45, 55-75 and 79-86 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/

Examiner, Art Unit 1623

/Shaojia Anna Jiang, Ph.D./

Supervisory Patent Examiner, Art Unit 1623